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EXAMINER	
ARCHIE, NINA	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPDOCKET@THOMPSONCOBURN.COM

Office Action Summary	Application No.	Applicant(s)	
	10/511,616	CURTISS, ROY	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9,10,26,31 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9,10,26,31 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/25/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 25, 2010 has been entered.

Amendment Entry

2. The amendment filed October 25, 2010 has been entered. Claims 1 and 31 have been amended. Claims 2 and 4, 11, and 21 are cancelled. Claims 1, 9-10, 26, and 31-32 are pending and currently under examination.

Information Disclosure Statement

4. The information disclosure statement filed 10/25/2010 has been considered. An initialed copy is enclosed.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

5. The rejection of claims 1, 9-10, 26, and 31-32 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for the reasons set forth in the previous office action. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicants arguments filed in response to the 35 U.S.C. 112 first paragraph, October 25, 2010 is carefully considered, but not found to be persuasive for the reasons below.

Applicant argues:

A) Applicants argue the claims are not drawn to a genus of LPS O-antigens, but rather to live attenuated strains of Salmonella that regulate synthesis of such LPS O-antigens. Applicants argue the claims indicate that it is the LPS core oligosaccharide antigen rather than the LPS O-antigen that is conserved. Applicants state the specification clearly outlines that "(t)he core region of LPS is highly conserved, in contrast to the O-antigen which is the basis for distinguishing the various serotypes of many Enterobacteriaceae species" (see first full paragraph page 18 of the specification as originally filed). Applicants state the specification further indicates that "LPS O-antigens are antigenically diverse as between strains of Enterobacteriaceae, and are a major factor in the variable immune response of host organisms to different strains of bacteria" (see second full paragraph on page 18 of the specification as originally filed). Applicant argue because claims are amended and drawn to "a regulatable $araCP_{BAD}$ promoter that is operably linked to a fur gene" and this specific $araCP_{BAD}$ promoter was known at the time of filing, structurally defined, and shown to function as per the claims in working examples provided by the Applicant, there is no reason to believe that one of ordinary skill in the art would doubt that the Applicant was in possession of the $araCP_{BAD}$ promoter.

B) Applicants state the variability of LPS O-antigens is also described in by the Reeves et al. reference that was cited in the specification (see Reeves, P. 1995. Role of O-Antigen Variation in the Immune Response. Trends Microbiol. 3:381-386 provided previously in IDS of October 1, 2007). Applicants state it is not at all clear that the Applicant should be required to demonstrate "any LPS O-antigen capable of being conserved among all Salmonella species and E.eoli strains" when the specification in fact indicates that such LPS O- antigens are not conserved and when the claims are not drawn in any way to "conserved" LPS-O antigens.

Applicant argue the state of the art with respect to LPS O-antigens and their regulation was well developed and extensive at the time of filing and given that LPS O-antigens and their regulation, like the immune-related DNA components of Capon v. Eshhar, were well known at

the time of filing, the specification need not provide an extensive set of LPS O-antigen sequences or correlation between the structure and function of LPS O-antigens to meet the written description requirement. Applicants argue at the time of filing, methods for regulating LPS O-antigen synthesis as claimed were extensively described in both the specification and literature referenced therein. Applicants argue regulation of LPS O-antigen synthesis could be predictably achieved by mutations in or regulation of genes of the rfb gene cluster as well as mutations in thepmi gene as described in the specification and literature cited therein. Furthermore, the state of the art with respect to conservation of the LPS core oligosaccharide across Salmonella and E. coli strains was also well developed at the time of filing (see Heinrichs et al., Molecular Microbiology (1998) 30(2), 221- 232 and Di Padova et al. (1993) Infect. Immun. 61(9):3863, both in the accompanying IDS).

C) Applicant state the Application as filed does disclose various means for regulating synthesis of LPS-O antigens as claimed. More specifically, the specification discloses both mutations in or regulation of genes of the rfb gene cluster as well as mutations in the pmi gene that are suitable for regulating expression of LPS O-antigens (on pages 12, 18-20). On page 20, the specification further indicates that such regulation can be achieved by replacing a promoter for any of the rfb genes that are needed for synthesis of the LPS O-antigen with the araCPgAD activator-repressor-promoter system. One of ordinary skill in the art would thus clearly understand that the Applicant was in possession of various means for regulating synthesis of LPS O-antigens as currently claimed.

Examiners Response to Applicants Arguments:

With regard to Points (A), (B), and (C), Applicant must adequately describe the claimed genus of LPS O-antigens capable of being exposed and conserved among all Salmonella species and capable of enhancing the ability to induce cross protective immunity against Salmonella species in an attenuated strain. The specification discloses OMP and IROMP antigens conserved among Enterobacteriaceae family that are capable of being synthesized caused by non-expression of an iron regulatory protein from fur gene in vivo and limited to LPS-O antigens conserved among Enterobacteriaceae family capable of ceasing synthesis in vivo. However, Applicants have only shown examples that demonstrate an increase in survivorship but not protection using specifically Salmonella typhimurium UK-1 Δpmi-2426

ΔPfur223::TTaraCP$_{BAD}$fur and challenged with wild-type Salmonella enteritidis wild type strain. Moreover, the specification is silent to which LPS O-antigens are capable of being conserved among all Salmonella species in an attenuated strain with enhanced ability to induce cross protective immunity against all Salmonella species. Moreover, the specification is silent with regard to what means must be employed to allow the LPS core oligosaccharide antigen its exposure in said attenuated strain? Consequently, the specification only disclose an attenuated Salmonella typhimurium UK-1 Δpmi-2426 ΔPfur223::TTaraCP$_{BAD}$fur strain challenged with wild-type Salmonella enteritidis strain but not cross-protective immunity against all Salmonella species. Moreover, Applicant has not shown the correlation between structure and function as it applies to the claimed genus LPS O-antigens. Thus, applicant was not in possession of the claimed genus. Thus, one of ordinary skill in the art would not understand that the Applicant was in possession of various means for regulating synthesis of LPS O-antigens as currently claimed. Moreover, the LPS O-antigens cited by applicant as being effective in an attenuated strain that has enhanced ability to induce cross-protective immunity against Salmonella all species are not representative of the claimed genus. Hence applicant's arguments are unpersuasive.

With regard to Point (B), Applicants assertion regarding the cited references aforementioned above is not persuasive because Applicants have only shown examples that demonstrate an increase in survivorship but not protection using specifically Salmonella typhimurium UK-1 Δpmi-2426 ΔPfur223::TTaraCP$_{BAD}$fur and challenged with wild-type Salmonella enteritidis wild type strain. Moreover, the specification is silent to which LPS O-antigens are capable of being conserved among all Salmonella species in an attenuated strain with enhanced ability to induce cross protective immunity against all Salmonella species. Moreover, the specification is silent with regard to what means must be employed to allow the LPS core oligosaccharide antigen its exposure in said attenuated strain? Consequently, the specification only disclose an attenuated Salmonella typhimurium UK-1 Δpmi-2426 ΔPfur223::TTaraCP$_{BAD}$fur strain challenged with wild-type Salmonella enteritidis strain but not cross-protective immunity against all Salmonella species. Therefore it is not at all how any LPS O-antigen is capable of being conserved among all Salmonella species.

As outlined previously, the claims are drawn to a vast genus of LPS O-antigens. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the

specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. Applicant must adequately describe the claimed genus of LPS O-antigens capable of being exposed and conserved among all Salmonella species and capable of enhancing the ability to induce cross protective immunity against Salmonella species in an attenuated strain.

The specification discloses bacterial strains that produce the group B LPS O-antigen side chains using slide agglutination assays within antisera resulting in moderate and high agglutination (see Table 4 pg. 33). The specification discloses a Salmonella typhimurium (S. typhimurium) strain χ8650 which demonstrates a function of time or number of generations of growth in nutrient broth medium in the absence of added mannose is a gradual loss of LPS O-antigen side chains (see pg. 33 second paragraph). Applicants disclose the administration of the S. typhimurium strain χ8650 with pmi mutation to mice and further observe the morbidity and mortality for 30 days, wherein the survivors from said strain were challenged with virulent wild-type S. typhimurium UK-1 χ3761 strain (see pg. 37), wherein the S. typhimurium strain χ8650 is grown in a nutrient broth medium in the absence of added mannose, which indicates a gradual loss of LPS O-antigen side chains that are reproduced in vivo in said strain after immunization of an animal host, enters visceral tissue. The specification disclosed the administration of S. typhimurium χ8754 strain and further challenge with virulent wild-type Salmonella enteritidis χ3700 strain (see pgs. 40-42), wherein the survivors from the challenge induced IgG antibodies to OMPs and IROMPs conserved among Enterobacteriaceae family (see pgs. 19 and 41-42). Therefore the specification discloses OMP and IROMP antigens conserved among Enterobacteriaceae family that are capable of being synthesized caused by non-expression of an iron regulatory protein from fur gene in vivo and limited to LPS-O antigens conserved among Enterobacteriaceae family capable of ceasing synthesis in vivo. However, Applicants have only shown examples that demonstrate an increase in survivorship but not protection using specifically Salmonella typhimurium UK-1 Δpmi-2426 ΔPfur223::TTaraCP$_{BAD}$fur and challenged with wild-type Salmonella enteritidis wild type strain. Moreover, the specification is

silent to which LPS O-antigens are capable of being conserved among all Salmonella species in an attenuated strain with enhanced ability to induce cross protective immunity against all Salmonella species. Moreover, the specification is silent with regard to what means must be employed to allow the LPS core oligosaccharide antigen its exposure in said attenuated strain? Consequently, the specification only disclose survival of subjects through the administration of an attenuated Salmonella typhimurium UK-1 Δpmi-2426 ΔPfur223::TTaraCP$_{BAD}$fur strain challenged with wild-type Salmonella enteritidis strain , but not cross-protective immunity against all Salmonella species.

Moreover, the claimed invention is drawn to cross-protective immunity against Salmonella species and as a result cross-protective immunity is correlated to a vaccine. A vaccine by definition must provide protection against an infection demonstrable by challenge experiments. The data as set forth supra does not demonstrate that the live attenuated derivative aforementioned above confers "protection" against infection by Salmonella species. Moreover, Applicant has not shown the correlation between structure and function as it applies to the claimed genus LPS O-antigens. Therefore the data fails to show or vaccine protection against Salmonella species. Therefore, one skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of a successful model. The working examples do not disclose any empirical data or results indicative of a preventing Salmonella infection as claimed. The specification is devoid of any teaching that the claimed attenuated strain prevents Salmonella infection. Thus, applicant was not in possession of the claimed genus.

The specification, does not disclose distinguishing and identifying features of a representative member of the genus of LPS O-antigens as to which the claims are drawn, such as a correlation between the structure of LPS O-antigens and its recited functions capable of being exposed and conserved among all Salmonella species and capable of enhancing the ability to induce cross protective immunity against Salmonella species in an attenuated strain, so that the skilled artisan could immediately envision or recognize at least a substantial number of members of the claimed genus of LPS O-antigens. Moreover, Applicant has not demonstrated any LPS O-antigen capable being conserved among all Salmonella species and capable of being exposed and conserved among all Salmonella species and capable of enhancing the ability to induce cross

protective immunity against Salmonella species in an attenuated strain. Therefore, the specification lacks written description of the instant claimed invention. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of regulators as to which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus aforementioned above.

MPEP § 2163.02 states, "an objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed". The courts have decided: The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. See Vas-Cath, Ink's. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "Written Description" Requirement (66 FR 1099-1111, January 5,2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104).

The Guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus.

Therefore, absent a detailed and particular description of a representative number of the members of the genus of LPS O-antigens, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of LPS O-antigens with the recited activities. Therefore, in accordance with the Guidelines, the description of any regulator is not deemed representative of the genus of regulators to which the claims refer and therefore the claimed invention is not properly disclosed.

Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Enablement

6. The rejection of 1, 9-10, 26, and 31-32 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons set forth in the previous Office Action. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants arguments filed in response to the 35 U.S.C. 112 first paragraph, October 25, 2010 is carefully considered, but not found to be persuasive for the reasons below.

Applicant arguments:

A) Applicants argue any of the Office's rejections based on an alleged lack of enablement of previously pending claim elements such as "vaccine" are also rendered moot. Applicant would respectfully request the Office provide an explanation as to what "prevention of Salmonella" might comprise, why working examples of 80-100% survivorship does not constitute an enhanced ability to induce cross-protective immunity against Salmonella specie as currently claimed, and what basis there is in the law for requiring that the claims enable a performance standard specified by the Office rather than the claims.

B) Applicants argue an examination of this case indicates that such representative examples, statements applicable to the genus as a whole, the level of skill, the state of the art and information in the specification indicate that live attenuated strains of Salmonella claimed herewith could be made and used without undue experimentation. Applicants state working examples where a live attenuated Salmonella strain provided an increase in survivorship following a challenge by virulent wild- type Salmonella strains of two distinct groups are provided in Examples 6 and 7. Applicants argue statements applicable to the genus of live attenuated Salmonella strains are found in at least the first paragraph of the Summary of Invention (page 11 of the specification), Example 1 (which provides a table of various Salmonella that includes groups B, C, D, and E), and Example 13 (which describes how to construct live attenuated strains of host-specific Salmonella serotypes of S. choleraesuis, S. dublin, S. paratyphi, and S. typhi using the same vectors and methods used to construct the exemplary strain). Applicants argue the level of skill in the field of live attenuated Salmonella

strains would typically comprise an individual with a doctoral degree who is versed in molecular and bacterial genetics and such an individual would have the advantage of operating at a point in time where the state of the art with respect to the field of live attenuated Salmonella strains, the $araCP_{BAD}$ activator-repressor-promoter system, fur genes, and regulation of LPS O- antigen genes was exceptionally well developed.

Applicants further maintain as per their previous Response that (t)he working examples do in fact provide empirical data or results indicative of a preventing Salmonella and E. coli infection as claimed, that the models provided in the specification are in fact art accepted as evidenced by their acceptance in peer reviewed scientific journals, that the Bolin et al. and Sood et al. references provided by the Office indicate that IROMPs apparently fall in that subset of antigens that result in a certain level of a protective response to infection and thus support enablement, and that the Greenspan et al. reference is irrelevant to enablement of the invention as currently claimed.

C) Applicants argue the state of the art was clearly advanced at the time of filing with respect to the $araCP_{BAD}$ activator-repressor-promoter system (Guzman et al., J.Bacteriol. 177:4121, 1995, cited on page 9 of the specification and provided previously in the IDS of October 1, 2007), Salmonella fur genes (Hall and Foster, J.Bacteriol. 178:5683, 1996, cited on page 8 of the specification and provided previously in the IDS of October 1, 2007), and regulation of LP S O-antigen synthesis (Collins et al., Infect. Immun. 59:1079, 1991, cited on page 7 of the specification and provided previously in the IDS of October 1, 2007). Finally, the specification itself provides significant guidance with respect to both $araCP_{BAD}$ activator-repressor-promoter system control of fur (see paragraph spanning page 21 and 22 of the specification as well as pages 29-30) and regulation of LPS O-antigen synthesis (see pages 12, 18-20 of the specification). Applicants argue these factors thus suggest that one skilled in art could, in light of the guidance provided by the specification, obtain any of the distinct Salmonella strains described in literature cited in the specification or elsewhere, place the fur gene of that strain under the control of an $araCP_{BAD}$ activator-repressor-promoter system, and regulate synthesis of the LPS O- antigen genes through nothing more than routine experimentation.

Examiners Response to Applicants Arguments:

With regard to Points (A) and (B), the claims encompassing any attenuated strain of Salmonella has enhanced ability to induce protective immunity against any Salmonella species is overly broad. The specification discloses the administration of S. typhimurium χ8754 strain and further challenge with virulent wild-type Salmonella enteritidis χ3700 strain (see pgs. 40-42), wherein the survivors from the challenge induced IgG antibodies to OMPs and IROMPs conserved among Enterobacteriaceae family (see pgs. 19 and 41-42). Therefore the specification discloses OMP and IROMP antigens conserved among Enterobacteriaceae family that are capable of being synthesized caused by non-expression of an iron regulatory protein from fur gene in vivo and limited to LPS-O antigens conserved among Enterobacteriaceae family capable of ceasing synthesis in vivo (see Examples 7-8). However, Applicants have only shown examples that demonstrate an increase in survivorship but not protection using specifically Salmonella typhimurium UK-1 Δpmi-2426 ΔPfur223::TTaraCP$_{BAD}$fur and challenged with wild-type Salmonella enteritidis wild type strain. Moreover, the specification is silent to which LPS O-antigens are capable of being conserved among all Salmonella species in an attenuated strain with enhanced ability to induce cross protective immunity against all Salmonella species. Moreover, the specification is silent with regard to what means must be employed to allow the LPS core oligosaccharide antigen its exposure in said attenuated strain? Consequently, the specification only disclose survival of subjects through the administration of an attenuated Salmonella typhimurium UK-1 Δpmi-2426 ΔPfur223::TTaraCP$_{BAD}$fur strain challenged with wild-type Salmonella enteritidis strain , but not cross-protective immunity against all Salmonella species.

Moreover, the claimed invention is drawn to cross-protective immunity against Salmonella species and as a result cross-protective immunity is correlated to a vaccine. A vaccine by definition must provide protection against an infection demonstrable by challenge experiments. The data as set forth supra does not demonstrate that the live attenuated derivative aforementioned above confers "protection" against infection by Salmonella species. Therefore Applicants assertion regarding Examples 20-22 regarding cross protective immunity are prophetic in nature and unpersuasive which fails to show vaccine protection against Salmonella species. Therefore, one skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of a successful model. The specification is

devoid of any teaching that the claimed attenuated strain prevents Salmonella infection. Thus, applicant was not in possession of the claimed genus.

With regard to Point (B), the claimed invention is drawn to cross-protective immunity against Salmonella species and as a result cross-protective immunity is correlated to a vaccine. A vaccine by definition must provide protection against an infection demonstrable by challenge experiments. The data as set forth supra does not demonstrate that the live attenuated derivative aforementioned above confers "protection" against infection by Salmonella species. Therefore Applicants assertion regarding Examples 20-22 regarding cross protective immunity are prophetic in nature and unpersuasive which fails to show vaccine protection against Salmonella species. The working examples do not disclose any empirical data or results indicative of a vaccine, therefore, one skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of a successful model. In regards to Applicants argument that the Examiner has not provided any specific evidence to suggest that the presently-claimed vaccine would not work, the Examiner has discussed the complexity of the vaccine art in the previous Office Action, therefore empirical data and or results from working examples indicative of a vaccine aforementioned above by definition would determine the success of the claimed invention.

With regard to Point (C), although there is guidance and the state of the art was clearly advanced at the time of filing with respect to the $araCP_{BAD}$ activator-repressor-promoter system, Applicants have only shown examples that demonstrate an increase in survivorship but not protection using specifically Salmonella typhimurium ΔPfur223::TTaraCP_{BAD}fur Δpmi-2426 strain. As stated in the previous office action, the state of the art has limitations and is unpredictable with regard to said attenuated strain with enhanced ability to induce protective immunity against Salmonella species. Therefore, the art is unpredictable with regard to a live attenuated strain of Salmonella typhimurium UK-1 Δpmi-2426 ΔPfur223::TTaraCP_{BAD}fur strain challenged with wild-type Salmonella enteritidis strain , with enhanced ability to induce protective immunity against Salmonella species.

As outlined previously, while being enabling for a Salmonella typhimurium UK-1 Δpmi-2426 ΔPfur223::TTaraCP_{BAD}fur strain comprising (a) a means for regulatable expression of a fur gene that encodes an iron regulatory protein, wherein said $araCP_{BAD}$ regulatable promoter is operably linked to said gene, wherein said gene is expressed when said attenuated strain is in the

intestinal tract of an individual and said gene is not expressed when said attenuated strain is within internal tissues of an individual and wherein non-expression of said iron regulatory protein in vivo causes synthesis of an antigen of outer membrane protein (OMP) or iron outer membrane protein (IROMP) that is conserved among the Enterobacteriaceae family, wherein said strain enhances the survival of an infection against Salmonella species and does not provide enablement for a live attenuated strain of Salmonella with enhanced ability to induce protective immunity against all Salmonella species and capable of being exposed and conserved among all Salmonella species comprising (a) a regulatable $araCP_{BAD}$ promoter that is operably linked to a fur gene, wherein said fur gene is expressed when said attenuated strain is in the intestinal tract of an individual and said gene is not expressed when said attenuated strain is within internal tissues of an individual and wherein non-expression of said fur gene in vivo causes synthesis of iron regulated outermembrane proteins (IROMP) and (b) a means for regulatable synthesis an LPS-O-antigen, wherein said LPS O-antigen ceases to be synthesized in vivo, exposing an LPS core oligosaccharide antigen that is conserved among Salmonella species.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

(A) The nature of the invention;

(B) The breadth of the claims;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention

The instant claims are drawn to a live attenuated strain of Salmonella comprising (a) a regulatable araCP$_{BAD}$ promoter that is operably linked to a fur gene, wherein said fur gene is expressed when said attenuated strain is in the intestinal tract of an individual and said gene is not expressed when said attenuated strain is within internal tissues of an individual and wherein non- expression of said fur gene in vivo causes synthesis of iron regulated outermembrane proteins (IROMP) and (b) a means for regulatable synthesis an LPS-O-antigen, wherein said LPS O-antigen ceases to be synthesized in vivo, exposing an LPS core oligosaccharide antigen that is conserved among Salmonella species; wherein said attenuated strain has enhanced ability to induce protective immunity against Salmonella species.

Breadth of the claims

The claims are overly broad. The claims encompass any live attenuated strain of any pathogenic Salmonella species with enhanced ability to induce protective immunity against all Salmonella species and capable of being exposed and conserved among all Salmonella species comprising (a) a regulatable araCP$_{BAD}$ promoter that is operably linked to a fur gene, wherein said fur gene is expressed when said attenuated strain is in the intestinal tract of an individual and said gene is not expressed when said attenuated strain is within internal tissues of an individual and wherein non-expression of said fur gene in vivo causes synthesis of iron regulated outermembrane proteins (IROMP) and (b) a means for regulatable synthesis an LPS-O-antigen, wherein said LPS O-antigen ceases to be synthesized in vivo, exposing an LPS core oligosaccharide antigen that is conserved among Salmonella species.

Guidance of the specification/The existence of working examples:

The specification discloses bacterial strains that produce the group B LPS O-antigen side chains using slide agglutination assays within antisera resulting in moderate and high agglutination (see Table 4 pg. 33). The specification discloses a Salmonella typhimurium (S. typhimurium) strain χ8650 which demonstrates a function of time or number of generations of growth in nutrient broth medium in the absence of added mannose is a gradual loss of LPS O-antigen side chains (see pg. 33 second paragraph). Applicants disclose the administration of the S. typhimurium strain χ8650 with pmi mutation to mice and further observe the morbidity and

mortality for 30 days, wherein the survivors from said strain were challenged with virulent wild-type S. typhimurium UK-1 χ3761 strain (see pg. 37), wherein the S. typhimurium strain χ8650 is grown in a nutrient broth medium in the absence of added mannose, which indicates a gradual loss of LPS O-antigen side chains that are reproduced in vivo in said strain after immunization of an animal host, enters visceral tissue. The specification disclosed the administration of S. typhimurium χ8754 strain and further challenge with virulent wild-type Salmonella enteritidis χ3700 strain (see pgs. 40-42), wherein the survivors from the challenge induced IgG antibodies to OMPs and IROMPs conserved among Enterobacteriaceae family (see pgs. 19 and 41-42). Therefore the specification discloses OMP and IROMP antigens conserved among Enterobacteriaceae family that are capable of being synthesized caused by non-expression of an iron regulatory protein from fur gene in vivo and limited to LPS-O antigens conserved among Enterobacteriaceae family capable of ceasing synthesis in vivo. However, Applicants have only shown examples that demonstrate an increase in survivorship but not protection using specifically Salmonella typhimurium UK-1 Δpmi-2426 ΔPfur223::TTaraCP$_{BAD}$fur and challenged with wild-type Salmonella enteritidis wild type strain. Moreover, the specification is silent to which LPS O-antigens are capable of being conserved among all Salmonella species in an attenuated strain with enhanced ability to induce cross protective immunity against all Salmonella species. Moreover, the specification is silent with regard to what means must be employed to allow the LPS core oligosaccharide antigen its exposure in said attenuated strain? Consequently, the specification only disclose survival of subjects through the administration of an attenuated Salmonella typhimurium UK-1 Δpmi-2426 ΔPfur223::TTaraCP$_{BAD}$fur strain challenged with wild-type Salmonella enteritidis strain , but not cross-protective immunity against all Salmonella species.

Moreover, the claimed invention is drawn to cross-protective immunity against Salmonella species and as a result cross-protective immunity is correlated to a vaccine. A vaccine by definition must provide protection against an infection demonstrable by challenge experiments. The data as set forth supra does not demonstrate that the live attenuated derivative aforementioned above confers "protection" against infection by Salmonella species. Therefore the data fails to show or vaccine protection against Salmonella species. Therefore, one skilled in the art would not accept on its face the examples given in the specification as being correlative or

representative of a successful model. The working examples do not disclose any empirical data or results indicative of a preventing Salmonella infection as claimed. The specification is devoid of any teaching that the claimed attenuated strain prevents Salmonella infection.

State of the art

The art discloses turkeys passively immunized with antibody against IROMPs of E. coli which significantly reduced the growth of bacteremia and the recovery of E. coli from air sacs thus increasing the survival of turkeys (see abstract and pg. 1242 specifically and Bolin et al 1987 Infection and Immunity pgs. 1239-1242 in its entirety). The art discloses mice passively immunized with antibody against IROMPs of Salmonella enterica serovar Typhi which significantly reduced the growth of bacteremia and increase the survival of mice and indicates that anti IROMPs antibodies may play an important role in providing protection at a systemic and mucosal level (see abstract and pgs. 69-71 and pg. 74 and Sood et al 2005 Molecular and Cellular Biochemistry Vol. 273 pgs. 69-78 in its entirety). Although many investigators have tried to develop vaccines based on specific antigens, it is well understood that the ability of an antigen to stimulate antibody production does not necessarily correlate with the ability of the antigen to stimulate an immune response capable of protecting an animal from infection (Chandrasekhar et al., US Patent 6,248,329, col. 1, and lines 35-41). It is well recognized in the vaccine art, that it is unclear whether an antigen derived from a pathogen will elicit protective immunity. Ellis (Chapter 29 of Vaccines, Plotkin, et al. (eds) WB Saunders, Philadelphia, 1998, especially p. 571, paragraph 2) exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.., and thus protect the host against attack by the pathogen." As evidenced by Greenspan et al. (Nature Biotechnology 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of

such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. For the reasons set forth supra, the state of the art is unpredictable with regard to said attenuated strain enhancing the ability to induce protective immunity against all Salmonella species.

In conclusion, the claimed invention does not provide enablement for a live attenuated strain of Salmonella with enhanced ability to induce protective immunity against all Salmonella species and capable of being exposed and conserved among all Salmonella species comprising (a) a regulatable $araCP_{BAD}$ promoter that is operably linked to a fur gene, wherein said fur gene is expressed when said attenuated strain is in the intestinal tract of an individual and said gene is not expressed when said attenuated strain is within internal tissues of an individual and wherein non-expression of said fur gene in vivo causes synthesis of iron regulated outermembrane proteins (IROMP) and (b) a means for regulatable synthesis an LPS-O-antigen, wherein said LPS O-antigen ceases to be synthesized in vivo, exposing an LPS core oligosaccharide antigen that is conserved among Salmonella species. Furthermore, the claims encompassing any live attenuated strain of any pathogenic Salmonella species comprising any live attenuated strain of any pathogenic Salmonella species with enhanced ability to induce protective immunity against all Salmonella species and capable of being exposed and conserved among all Salmonella species is overly broad. The specification fails to teach that said attenuated strain as set forth can produce a protective response in a host, for prevention of Salmonella which is a requisite of a vaccine. The specification discloses examples that demonstrate an increase in survivorship using specifically Salmonella typhimurium UK-1 Δpmi-2426 ΔPfur223::$TTaraCP_{BAD}$fur and challenged with wild-type Salmonella enteritidis wild type strain but not cross-protective immunity against all Salmonella species. Moreover, the specification is silent to which LPS O-antigens are capable of being conserved among all Salmonella species in an attenuated strain with enhanced ability to induce cross protective immunity against all Salmonella species. Moreover, the specification is silent with regard to what means must be employed to allow the LPS core oligosaccharide antigen its exposure in said attenuated strain? Furthermore, the state of the art teaches that there are limitations to a vaccine and the state of the art is unpredictable. Therefore, in view of the lack of support in the art and specification regarding which LPS O-antigens are capable of being

conserved among all Salmonella species and to what means must be employed to allow the LPS core oligosaccharide antigen its exposure in said attenuated strain for an effective vaccine, it would require undue experimentation on the part of the skilled artisan to make and use the vaccine as claimed; therefore the claims are not enabled. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed composition.

Conclusion

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Patricia Duffy can be reached on 571-272-0855. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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